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2. Studies of Cancer in Humans

2.1 Occupational exposure

2.1.1 *Talc miners and millers* (Table 2.1)

Rubino *et al.* (1976) conducted a study of mortality among men who had begun work in the mines and mills of a talc operation in the Germanasca and Chisone valleys (Piedmont), Italy, between 1921 and 1950 and who had been employed for at least 1 year in a job that involved exposure to talc. A total of 1514 miners and 478 millers were identified, of whom 168 miners (11.1%) and 40 millers (8.4%) were lost to follow-up before the end of the study in June 1974, yielding a combined cohort of 1784 men (89.6%) for analysis. The talc from these mines was described as pure and was reported to have been used in the pharmaceutical and cosmetics industries. However, due to the presence of 'footwall contact rocks' and rock-type inclusions in the mines, drilling operations were associated with exposure to dusts that contained high levels of silica; such inclusions were removed before milling and talc products were reported to have a content of free silica below 2%. [The Working Group understood that the term 'silica' was in fact quartz.] In a few instances, talc samples from the area showed small amounts of tremolite when examined by X-ray diffraction, but no amphibolic asbestos or chrysotile were detected. For each worker, cumulative exposure was estimated from regular measurements of respirable dust content in the air of mines and mills during the period 1948–74 and individual work histories were abstracted from files of the mining company. Periods of time during which the dust level was assumed to be uniform were first selected and cumulative exposure was then calculated as the summed product of the number of years in each specific working period (years) and the associated dust levels (million particles per cubic foot; mppcf), resulting in an overall measure of mppcf–years. Once individual cumulative exposures had been assigned, miners and millers were then classified separately into low, medium and high levels of exposure. Ranges of exposure (mppcf–years) for miners were 566–1699, 1700–5665 and 5666–12750, respectively; ranges of exposure for millers were 25–141, 142–424 and 425–906, respectively. For each of the 1784 workers included (1346 miners and 438 millers), one unexposed control subject was chosen at random from among male inhabitants of a nearby small, rural town. The control was matched to the talc worker on year of birth and vital status at date of entry into the study [date not specified]. Cause of death for 885 (95.1%) of 931 deceased workers and 1067 (94.8%) of 1126 deceased controls was obtained from regional death certificate files supplemented with information from relatives, physicians and medical records. Observed numbers of deaths among talc workers were compared with expected numbers, calculated by the use of age-specific mortality rates experienced by the control cohort. The standardized mortality ratio (SMR) for all causes combined was 0.9 (95%

Table 2.1. Cohort studies of mortality from and incidence of cancer in populations occupationally exposed to non-asbestiform talc

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors; comments
Rubino *et al.* (1976), Germanesca and Chisone valleys (Piedmont), Italy	1992 male talc workers (1514 miners, 478 millers) employed >1 year in talc-exposed job during 1921–1974; hired 1921–1950; mortality follow-up, 1921–74; vital status, 90%; cause of death: 95% of exposed workers, 95% of controls	Occupational history from plant records; respirable dust measurements, 1948–1974; quantitative estimation of cumulative exposure for individual workers, expressed as summed product of duration (years) and exposure (million particles per cubic foot, mppcf); classification of workers into 3 levels of exposure	All cancers	All miners	100	**SMR** 0.8 (0.6–0.9)	Adjusted for age; comparison with unexposed, age-matched controls from neighbouring rural town; controls matched on vital status at date of entry into study; miners and millers exposed to a very pure form of talc; miners also exposed to inhalable silica; significantly elevated SMRs for silicosis with and without tuberculosis among miners; estimates increased with increasing cumulative exposure; no observed cases of mesothelioma; no smoking data for exposed workers or unexposed controls
				All millers	42	0.9 (0.7–1.2)	
				Miners (mppcf–years)			
				Level 1: 566–1699	38	1.2 (0.8–1.6)	
				Level 2: 1700–5665	28	1.0 (0.7–1.4)	
				Level 3: 5666–12750	34	0.9 (0.6–1.2)	
				Millers (mppcf–years)			
				Level 1: 25–141	18	1.1 (0.2–3.2)	
				Level 2: 142–424	13	1.3 (0–2.9)	
				Level 3: 425–906	11	0.7 (0.4–2.7)	
			Lung, bronchus and trachea	All miners	9	0.5 (0.2–0.9)	
				All millers	4	0.6 (0.2–1.6)	
				Miners (mppcf–years)			
				Level 1: 566–1699	3	1.1 (0.6–1.7)	
				Level 2: 1700–5665	1	0.5 (0.7–2.3)	
				Level 3: 5666–12750	5	1.1 (0.4–1.3)	
				Millers (mppcf–years)			
				Level 1: 25–141	3	1.7 (0.3–4.9)	
				Level 2: 142–424	1	1.25 (0–7.0)	
				Level 3: 425–906	0	–	

Table 2.1 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors; comments
Rubino *et al.* (1979), Germanesca and Chisone valleys (Piedmont), Italy	1678 male talc workers (1260 miners, 418 millers); mortality follow-up, 1946–74	Same exposure categories as Rubino *et al.* (1976)	Lung			**SMR**	Re-analysis of cohort reported in Rubino *et al.* (1976); SMRs recalculated using national death rates instead of comparison with neighbouring rural population; national death rates available only from 1951 onward; rates for 1951 were applied for 1946–50
				All miners	8	0.5 (0.2–0.9)	
				All millers	4	0.7 (0.2–1.7)	
				Miners (mppcf–years)			
				Level 1: 566–1699	2	0.5 (0–1.9)	
				Level 2: 1700–5665	1	0.2 (0.5–1.2)	
				Level 3: 5666–12750	5	0.6 (0.2–1.4)	
				Millers (mppcf–years)			
				Level 1: 25–141	3	2.0 (0.4–5.8)	
				Level 2: 142–424	1	0.7 (1.7–3.7)	
				Level 3: 425–906	0	–	
Selevan *et al.* (1979), Vermont, USA	392 white male talc workers (163 miners, 225 millers) employed >1 year between 1940 and 1969; mortality follow-up: date of first radiogram, 12-month employment anniversary or January 1940, whichever was later; follow-up through 1975; vital status: 99%; cause of death: 94%	Historical insufficient information to calculate cumulative exposure histories; cohort classified into two work areas: mining and milling.				**SMR**	Adjusted for age, sex, race, calendar year; US death rates: 1940–67; linear extrapolation for all causes of death: 1967–69. Vermont death rates for specific causes of death: 1949–75; workers selected from annual radiographic survey of dusty trades; no data on smoking habits for millers or miners; exposure to radon daughters in mine; radiographic evidence of pneumoconiosis in most workers who died from non-malignant respiratory disease
			All causes	Total cohort	90	1.2 [0.9–1.4]	
				Millers	44	1.2 [0.9–1.6]	
				Miners	34	1.3 [0.9–1.8]	
			All cancers	Total cohort	16	[1.3 (0.7– 2.0)]	
				Millers	5	[0.8 (0.3–1.9)]	
				Miners	7	[1.7 (0.7–3.5)]	
			Respiratory cancer	Total cohort	6	[1.6 (0.6–3.5)]	
				Millers	2	[1.0 (0.1–3.7)]	
				Miners	5	[4.3 (1.4–10.1)]	

Table 2.1 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors; comments
Wergeland *et al*. (1990), northern and western Norway	389 male talc-exposed workers (94 miners, 295 millers) employed >1 year in mine (1944–72) or >2 years in mill (1935–72); mortality and cancer incidence follow-up; 1953–87	Subjective assessment of exposure by experienced colleagues; workers classified by total duration of employment in jobs with low, medium, high and unknown exposure				**SMR**	Adjusted for age, smoking (miners only); national death rates: 1953–87; main minerals in mined talc deposit were talc and magnesite; 90% of raw material for mill from mine; 10% from India; no information on smoking habits for millers; smoking habits for miners above national average; low levels of exposure to radon daughters
			All causes	*Total cohort*	117	0.8 (0.6–0.9)	
				Miners	27	[0.8 (0.5–1.2)]	
				Millers	90	[0.7 (0.6–0.9)]	
			All cancers	*Total cohort*	26	0.8 (0.5–1.1)	
				Miners	9	[1.3 (0.6–2.5)]	
				Millers	17	[0.6 (0.4–1.0)]	
						SIR	
			All cancers	*Total cohort*	46	0.9 (0.7–1.2)	
				Miners	15	[1.4 (0.8–2.3)]	
				Millers	31	[0.8 (0.5–1.1)]	
				Years employed			
				1–4	11	[1.1 (0.6–2.1)]	
				5–19	19	[0.8 (0.5–1.2)]	
				>20	16	[0.9 (0.5–1.5)]	
				Years since first employment			
				1–19	6	[0.4 (0.2–0.9)]	
				20–29	18	[1.1 (0.7–1.8)]	
				>30	22	[1.1 (0.7–1.6)]	

Table 2.1 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors; comments
Wergeland *et al*. (1990) (contd)			Lung	*Total cohort*	6	0.9 (0.3–2.0)	
				Miners	2	[1.6 (0.2–5.7)]	
				Millers	4	[0.8 (0.2–2.0)]	
				Years employed			
				1–4	0	–	
				5–19	3	[1.0 (0.2–3.0)]	
				>20	3	[1.0 (0.2–3.0)]	
				Years since first employment			
				1–19	2	[1.1 (0.1–4.1)]	
				20–29	1	[0.5 (1.3–2.8)]	
				>30	3	[1.1 (0.2–3.2)]	
			Stomach	*Total cohort*	6	1.1 (0.4–2.2)	
				Miners	3	[2.5 (0.5–7.4)]	
				Millers	3	[0.7 (0.1–2.1)]	
				Years employed			
				1–4	2	[2.0 (0.2–7.2)]	
				5–19	2	[0.8 (0.1–2.6)]	
				>20	2	[1.2 (0.1–4.3)]	
				Years since first employment			
				1–19	1	[0.6 (1.4–3.1)]	
				20–29	2	[1.1 (0.1–4.0)]	
				>30	3	[1.7 (0.3–4.8)]	

Table 2.1 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors; comments
Wild (2000), Luzenac, France	1160 talc workers (1070 men, 90 women) actively employed in 1945 or hired during 1945–94 and employed >1 year; mortality follow-up,,1945–96; vital status: 97%; cause of death: 74% pre-1968 and 98% post-1968	Exposures assessed for case–control study; semi-quantitative, site-specific job-exposure matrix based on personal dust measurements (1986 onwards) and subjective assessments by experienced workers; workers assigned to four categories of exposure: no exposure, ambient (<5 mg/m^3), medium (5–30 mg/m^3) and high (>30 mg/m^3); exposure prior to hiring also coded: none, probable exposure to quartz, certain exposure to quartz, exposure to other carcinogens.		*Male talc workers*		**SMR**	Adjusted for age, sex, smoking, prior exposure to quartz (case–control study only); partial overlap of study population with Leophonte *et al.* (1983) and Leophonte and Didier (1990); extent of overlap unknown; national mortality rates applied: pre- and post-1968; regional mortality rates applied: post-1968: excess mortality from lung cancer disappeared when national rates applied
			All causes	Pre-1968 (national rates)	101	0.8 (0.6–1.0)	
				Post-1968 (national rates)	294	0.8 (0.7–0.9)	
				Post-1968 (regional rates)	294	0.9 (0.8–1.0)	
			All cancers	Post-1968 (regional rates)	80	1.0 (0.8–1.3)	
			Lung	Post-1968 (regional rates)	21	1.2 (0.8–1.9)	
				Post-1968 (national rates)	21	0.9 (0.6–1.4)	
				Men <60 years of age	7	2.0 [0.8–4.0]	
				Latency period <20 years	5	2.4 [0.8–5.6]	
				Duration of employment <10 years	8	2.1 [0.9–4.1]	
			Stomach	Post-1968 (national rates)	5	1.2 (0.4–2.8)	

Table 2.1 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors; comments
Wild (2000) (contd)	Nested case–control study: lung cancer, non-malignant pulmonary disease and stomach cancer; three randomly selected controls per case; lung cancer: 23 cases, 67 controls	Cumulative exposure estimates (mg/m^3–years) for individual workers.	Lung			**Odds ratio**	Unadjusted odds ratio; no increasing trend with increasing cumulative exposure; information on smoking habits available for 52% of cases and 75% of controls Assumes a linear trend
				Unexposed	6	1.0	
				<100 mg/m^3–years	5	1.4	
				100–400 mg/m^3–years	6	2.2	
				400–800 mg/m^3–years	3	0.7	
				>800 mg/m^3–years	3	0.9	
				Per 100 mg/m^3–years	23	1.0 (0.9–1.1)	
Wild *et al.* (2002), Luzenac, France (1 site), and Styrian Alps, Austria (4 sites)	Austrian cohort: 542 male talc workers employed >1 year during 1972–95; mortality follow-up, 1972–1995; vital status: 97%;. French cohort: as described under Wild (2000)	Austrian cohort: semi-quantitative, site-specific job-exposure matrix based on personal dust measurements (1988–92) and descriptions of workplaces from management and long-term workers; workers assigned to four categories of exposure: no exposure, ambient (<5 mg/m^3), medium (5–30 mg/m^3) and high (>30 mg/m^3); other exposures coded: quartz, other carcinogens, underground work				**SMR**	Adjusted for age, calendar year, smoking, exposure to quartz, exposure to other carcinogens, underground work (case–control study); study population overlaps with that of Wild (2000); French SMRs calculated by comparison with regional rates, 1968–95; Austrian SMRs calculated by comparison with regional rates, 1972–1995; Austrian smoking information obtained from unpublished mortality studies on pneumoconiosis, from colleagues, from workers' compensation records; no missing information on smoking habits in Austrian cohort
			All causes	French cohort	294	0.9 (0.8–1.0)	
				Austrian cohort	67	0.8 (0.6–1.0)	
			All cancers	French cohort	80	1.0 (0.8–1.3)	
				Austrian cohort	17	0.7 (0.4–1.2)	
			Lung	French cohort	21	1.2 (0.8–1.9)	
				Austrian cohort	7	1.1 (0.4–2.2)	
			Stomach	French cohort	5	1.2 (0.4–2.8)	
				Austrian cohort	1	0.4 (0–2.3)	

Table 2.1 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors; comments
Wild *et al.* (2002) (contd)	Nested case–control study: lung cancer, non-malignant respiratory disease; three randomly selected controls per case; lung cancer: 23 cases, 67 controls (France); 7 cases, 21 controls (Austria)	Cumulative exposure estimates (mg/m^3–years) assigned to individual workers by occupational physician using work histories abstracted from company records	Lung			**Odds ratio**	Unadjusted odds ratio; no trend observed with increasing cumulative exposure; trend not affected by adjusting for smoking, quartz exposure, underground work or by lagging the exposure estimate
				Unexposed	9	1.0	
				≤100 mg/m^3–years	6	0.9	
				101–400 mg/m^3–years	7	1.1	
				401–800 mg/m^3–years	5	0.6	
				>801 mg/m^3–years	3	0.7	
				Per 100 mg/m^3–years	30	1.0 (0.9–1.1)	Assumes a linear trend
Coggiola *et al.* (2003), Piedmont, Italy	Cohort of 1974 male talc workers employed >1 year in mine or mill during 1946–95; mortality follow-up, 1946–95; loss to follow-up, 9%; analysis based on 1244 miners, 551 millers	Detailed job histories from plant records; workers classified on basis of job held (miner versus miller), duration of exposure (years) and time since first exposure (years)				**SMR**	Adjusted for age, calendar period; study population overlaps with that of Rubino *et al.* (1976, 1979); national death rates used for pre-1970 period; rates for early 1950s used for 1946–49; regional rates used for 1970–95, except for cancers of oral cavity, oesophagus and suicide (regional rates unavailable, national rates used); no information on smoking habits; no variation in lung cancer by duration of exposure
			All causes	Total cohort	880	1.2 (1.1–1.3)	
				Miners	590	1.3 (1.2–1.4)	
				Millers	290	1.1 (1.0–1.2)	
			All cancers	Total cohort	185	1.0 (0.9–1.1)	
				Miners	130	1.1 (1.0–1.3)	
				Millers	55	0.9 (0.6–1.1)	
			Lung cancer	Total cohort	44	0.9 (0.7–1.3)	
				Miners	33	1.1 (0.7–1.5)	
				Millers	11	0.7 (0.3–1.2)	
				Years since first exposure			
				<20	6	1.1 (0.4–2.3)	
				20–30	10	1.0 (0.5–1.8)	
				>30	28	0.9 (0.6–1.3)	

Table 2.1 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors; comments
Coggiola *et al*. (contd)						**SMR**	
			Oral cavity	Total cohort	31	5.1 (3.5–7.3)	
				Miners	24	6.2 (3.9–9.1)	
				Millers	7	3.3 (1.3–6.9)	
			Oesophagus	Total cohort	10	2.1 (1.1–3.9)	
				Miners	7	2.3 (0.9–4.8)	
				Millers	3	1.8 (0.4–5.2)	
			Stomach	Total cohort	31	1.2 (0.8–1.6)	
				Miners	20	1.2 (0.7–1.8)	
				Millers	11	1.1 (0.5–2.0)	

CI, confidence interval; mppcf, million parts per cubic foot; SIR, standardized incidence ratio; SMR, standardized mortality ratio

confidence interval (CI), 0.8–1.0) for miners and 0.9 (95% CI, 0.8–1.0) for millers. No relationship was observed with increasing time between first exposure and death or with increasing cumulative exposure. Significant increases in specific cause of death among miners were found for silicosis (62 observed; SMR, 2.0; (95% CI, 1.5–2.6) and for silicosis with superimposed tuberculosis (18 observed; SMR, 2.0; 95% CI, 1.2–3.1). These estimates were found to increase with increasing cumulative exposure. A total of 100 deaths from cancers at all sites combined among miners (SMR, 0.8; 95% CI, 0.6–0.9) and 42 deaths among millers (SMR, 0.9; 95% CI, 0.7–1.2) were below those expected. Nine deaths among miners (SMR, 0.5; 95% CI, 0.2–0.9) and four among millers (SMR, 0.6; 95% CI, 0.2–1.6) were due to lung cancer. No excess risk for lung cancer was found in the highest exposure category among miners (cumulative exposure range, 5666–12750 mppcf–years; five observed; SMR, 1.1; 95% CI, 0.4–2.7) or millers (cumulative exposure range, 425–906 mppcf–years; no observed deaths versus 1.3 expected). No cases of mesothelioma were found. [The Working Group noted that the lack of comparability between the workers and the comparison groups could influence the mortality ratio estimates of this study.]

In a re-analysis of their 1976 study, Rubino *et al.* (1979) estimated relative mortality among talc workers using Italian national death rates for men instead of the control cohort. As national rates were available only for the period 1951–74 (end of the study), rates for 1951 were applied for the follow-up period 1946 through to 1950. The number of workers included in this analysis was 1260 miners and 418 millers. In contrast to the previous analysis, the age-standardized mortality for all causes combined was significantly increased for miners (560 observed; SMR, 1.3; 95% CI, 1.2–1.4) as well as for millers (193 observed; SMR, 1.2; 95% CI, 1.0–1.4). Eight observed cases of lung cancer in miners yielded an SMR of 0.5 (95% CI, 0.2–0.9) and four cases in millers yielded an SMR of 0.7 (95% CI, 0.2–1.7). No trend was observed with increasing cumulative exposure for either group of workers [*p*-value for trend not provided]. Mortality from non-malignant respiratory diseases was significantly increased among miners (109 observed; SMR, 3.3; 95% CI, 2.7–4.0), mainly due to 58 cases of pneumoconiosis and 23 cases of tuberculosis. The number of cases of pneumoconiosis and tuberculosis among millers was three and eight, respectively.

Katsnelson and Mokronosova (1979) conducted a study of mortality among male and female workers [numbers not specified] in a talc mining and processing plant in the former USSR in 1949–75. The talc of the area was reported to contain no tremolite or fibrous materials and levels of quartz ranged from 0.2 to 1.6%. Very high mortality ratios were found for cancer at all sites combined (relative risks, 5.1 for men; 6.4 for women; $P < 0.001$) as well as for lung (relative risks, 4.5 for men; $P < 0.02$; 9.3 for women; $P > 0.05$) and stomach cancer (relative risks, 3.7 for men; $P < 0.02$; 6.3 for women; $P < 0.05$) [observed numbers of deaths not specified]. [The Working Group noted that the deaths observed among exposed workers included current and past workers but that the denominator comprised only currently employed persons.]

Selevan *et al.* (1979) used radiography records from the annual surveys of workers in dusty trades of the Vermont Health Department to identify all white male workers employed in the Vermont talc industry for at least 1 year between 1940 and 1969. The study covered three areas that had a total of five companies (two of which ceased operations in 1952 and 1960). The talc in this region is a mixture of pure talc, magnesite, chlorite and dolomite. Airborne dust samples and bulk materials were free of asbestiform minerals, when examined by both X-ray diffraction and analytical electron microscopy. Levels of respirable crystalline silica were below 0.25% in nearly all ore and product samples, and free silica was only occasionally detectable in air samples. Insufficient information was available to estimate cumulative lifetime exposures, but the authors stated that historical data were sufficient to demonstrate past exposure levels for miners and millers far exceeded the standard for non-fibrous talc of 20 mppcf that was in force at the time of the investigation. Due to the more continuous nature of the milling operation, it was considered probable that exposures to dust for millers were higher than those for miners. In one mine that had closed by the time of the study, 'cobblestones' of highly tremolitic serpentine rock were present but were avoided or discarded as far as possible before milling. Miners were also exposed to radon daughters at mean levels ranging up to 0.12 working levels (WL), with single peaks of 1.0 WL. The study groups comprised 163 talc miners and 225 millers. Vital status of workers was ascertained through to 1975, and death certificates were obtained for 85 of 90 deceased cohort members. For non-malignant respiratory disease and respiratory cancer, mortality rates for white men from Vermont were used for comparison, because they were considered to be more appropriate than national rates. For other causes of death, rates for the USA were used. Some increase was noted for all malignant neoplasms combined (16 observed [SMR, 1.3; 95% CI, 0.7–2.0]) and specifically for respiratory cancer (six observed [SMR, 1.6; 95% CI, 0.6–3.5]). [The Working Group noted that the results for respiratory cancer were not analysed by latency.] The excess mortality from respiratory cancer was statistically significant among the miners (five observed [SMR, 4.3; 95% CI, 1.4–10.1]), but not among the millers (two observed [SMR, 1.0; 95% CI, 0.1–3.7]). A significant excess of mortality from non-malignant respiratory disease was seen in millers (seven observed [SMR, 4.1; 95% CI, 1.6–8.4]), but not in miners (two observed [SMR, 1.6; 95% CI, 0.2–5.9]). Most workers who died from non-malignant respiratory disease had radiographic evidence of pneumoconiosis (rounded opacities).

In two brief communications, Leophonte *et al.* (1983) and Leophonte and Didier (1990) reported on the mortality of workers employed in a talc quarry in Luzenac in the South of France and in the associated talc processing plant. The cohort was composed of those who left employment between 1945 and 1981 and who had worked at the plant for more than 1 year. The talc in this region is a mixture of pure talc, chlorite and dolomite with no asbestos; levels of quartz vary from 0.5 to 3%. Of 470 workers available for study, 256 were alive, 209 had died and five were lost to follow-up. Of 204 workers with a known job history and date of death, 192 had worked exclusively with talc at Luzenac. No significant excess of mortality from cancer in general or specifically from respiratory

and digestive cancers was found. [Observed and expected numbers of cause-specific deaths and associated relative risks were not given.] A significant increase in mortality was found for non-malignant respiratory disease, especially for pneumoconiosis and obstructive lung disease. No cases of mesothelioma were observed. [The Working Group noted the unconventional definition of the cohort and that causes of death were obtained differently for cases (from local doctors, hospitals or families) and controls (from regional or national records).]

Wergeland *et al.* (1990) studied 94 male workers at a talc mine in northern Norway who had been employed in talc-exposed jobs for at least 1 year during 1944–72 and 295 male workers at a talc mill in western Norway who had been employed for at least 2 years during 1935–72. Data on miners were gathered from the company pay rolls, lists of union memberships and the central registry of workers exposed to silica in Norway; data on millers were collected from the company protocol and the local occupational health service. The information included name, date of birth, first and last date of employment and number of periods of employment. According to the authors, Norwegian talc contains only trace quantities of quartz, tremolite and anthophyllite as determined by optical microscopy and by electron microscopic analysis. The talc in the region where the mine was located is composed mainly of pure talc and magnesite. Approximately 90% of the raw material in the mill came from the mine and the rest was imported from India. In addition to talc, dolomite and mica were also processed at the mill. Personal air samples collected in the early 1980s showed that total dust levels varied greatly by job category and workplace (mine, 0.9–97 mg/m^3; mill, 1.4–54 mg/m^3). Peak exposures occurred during drilling in the mine (319 mg/m^3) and in the store house in the mill (109 mg/m^3). X-Ray diffractometry indicated that dust samples from both operations contained less than 1% quartz. The mean value for concentrations of radon daughters in the mine was 3.5 pCi/L [0.04 WL], with a range of 1.5–7.5 pCi/L [0.02–0.08 WL]. The majority of the 389 workers could be classified into one of three categories according to degree of dust exposure, based on measurements and qualified assessments of dust level by experienced co-workers. Information on tobacco smoking habits, gathered during the study in 1981, was available for 63 of the 94 miners and showed that smoking rates among these workers were above the national average. Follow-up for cancer incidence (through data linkage to the national cancer registry) and cause-specific mortality (through linkage to the national mortality files) was begun at the date of entry into the cohort or 1 January 1953, whichever came later, and ended at date of death or 31 December 1987, whichever came first. National rates were used to calculate expected numbers of cancers and deaths. The SMR for all causes for the total cohort was 0.8 (117 observed; 95% CI, 0.6–0.9), which reflected a decrease among both miners (27 observed [SMR, 0.8; 95% CI, 0.5–1.2]) and millers (90 observed [SMR, 0.7; 95% CI; 0.6–0.9]). An excess of deaths from all cancers was observed in miners (nine observed [SMR, 1.3; 95% CI, 0.6–2.5]), but not in either the total cohort (26 observed [SMR, 0.8; 95% CI; 0.5–1.1]) or in millers (17 observed; [SMR, 0.6; 95% CI; 0.4–1.0]). Mortality from non-malignant respiratory diseases was decreased, with one observed death among miners [SMR, 0.4; 95% CI, 0–

2.2] and two observed deaths among millers [SMR, 0.2; 95% CI, 0–0.9]. No deaths from pneumoconiosis were reported. The standardized incidence ratio (SIR) for all types of cancer combined was [1.4 (15 observed; 95% CI, 0.8–2.3)] among the miners and [0.8 (31 observed; 95% CI, 0.5–1.1)] among the millers. Two cases of lung cancer were observed among miners [SIR, 1.6; 95% CI, 0.2–5.7] and four cases among millers [SIR, 0.8; 95% CI, 0.2–2.0]. The non-significant excess risk among the miners was confined to cancer of the stomach (three observed [SIR, 2.5; 95% CI, 0.5–7.4]) and cancer of the prostate (four observed [SIR, 2.0; 95% CI, 0.6–5.2]). In the subgroup of 80 workers who belonged to the highest exposure category, a total of six cases of cancer were observed [SIR, 0.4; 95% CI, 0.2–1.0], none of which were cancer of the lung. There were no observed cases of mesothelioma.

Wild (2000) conducted a retrospective cohort mortality study, within a nested case-control study, at the same talc quarry and milling plant at Luzenac as that used by Leophonte *et al.* (1983) and Leophonte and Didier (1990). The cohort included employees who were active in 1945 or hired in the milling plant during the period 1945–94 and who had been employed continuously for at least 1 year. Employees, who were identified from the company files, comprised a total of 1070 men and 90 women. [The authors did not indicate the extent of overlap of the study population with that investigated by Leophonte *et al.* (1983) and Leophonte and Didier (1990).] Dust levels in the 1960s and 1970s were generally high, ranging from below 5 mg/m^3 to more than 30 mg/m^3. Average dust levels dropped to below 5 mg/m^3 in the 1990s through process changes and installation of engineering controls (e.g. installation of a central vacuum system). Overall mortality of the cohort was evaluated from 1 January 1945 to 31 December 1996. Vital status was obtained from the local population register and national mortality files which also included information on cause of death, in most cases, for individuals who died after 1968. Overall, 32 (2.8%) employees were lost to follow-up. Of 106 individuals who died before 1968, cause of death was ascertained for 78 cases. SMRs were calculated using both regional mortality rates (pre- and post-1968) and national mortality rates (pre-1968). When regional mortality rates for 1968 and later were used, the SMR for all causes of death combined was 0.9 (294 observed; 95% CI, 0.8–1.0) for men and 0.8 (11 observed; 95% CI, 0.4–1.4) for women. Eighty men died from cancer at any site (SMR, 1.0; 95% CI, 0.8–1.3) and 21 died from lung cancer specifically (SMR, 1.2; 95% CI, 0.8–1.9). Mortality from lung cancer was non-significantly increased in subgroups of employees who were under 60 years of age (seven observed; SMR, 2.0 [95% CI, 0.8–4.0]), had a latency period of less than 20 years (five observed; SMR, 2.4 [95% CI, 0.8–5.6]) or had a duration of employment of less than 10 years (eight observed; SMR, 2.1 [95% CI, 0.9–4.1]). A slightly increased risk was seen for stomach cancer (five observed; SMR, 1.2; 95% CI, 0.4–2.8). Twenty-six men died from non-malignant respiratory diseases (SMR, 1.1; 95% CI, 0.7–1.6), three of which were pneumoconiosis (SMR, 5.6; 95% CI, 1.1–16.2). When pre-1968 national reference rates were applied, the overall SMR for men was 0.8 (101 observed; 95% CI, 0.6–1.0) and the excess mortality from lung cancer and non-malignant respiratory diseases disappeared. Of

the 101 deaths observed during this period, one was caused by lung cancer (SMR, 0.3 [95% CI, 0.7–1.5]) and five were caused by non-malignant respiratory diseases (SMR, 0.7 [95% CI, 0.2–1.6]). A nested case–control study was performed to investigate further the risks for lung cancer, stomach cancer and non-malignant respiratory diseases in the men of the cohort. For the lung cancer case–control study, 67 controls were individually matched to the 22 cases by age and sex (approximately three controls per case). Information on job history at the plant and tobacco consumption was collected through interviews of subjects who were alive and/or from experienced co-workers. A semiquantitative site-specific job–exposure matrix for talc dust was established using dust levels measured from 1986 onwards and estimates of levels before that year. Information on job history was then converted into estimates of cumulative exposure of the individual employees (expressed as mg/m^3–years). Multiple logistic regression analysis with adjustment for tobacco smoking habits and exposure to quartz estimated the odds ratio for lung cancer to be 0.7 (three cases and 15 controls) and 0.9 (three cases and 10 controls) for employees with a cumulative exposure to talc dust of 400–800 mg/m^3–years and more than 800 mg/m^3–years, respectively, when compared with unexposed employees (six cases and 20 controls). [The Working Group noted that information on smoking habits was available for only 52% of cases and 75% of controls, and that no specific information was given on the proportion of subjects alive among cases and controls at the date of interview.]

Wild *et al.* (2002) conducted a combined analysis of previously published cohort mortality studies among 1070 male employees at a talc quarry and milling plant in the south of France (Site A) (Wild, 2000) and 542 male employees at three talc mines and their respective mills in Austria (Sites B, C and D). The Austrian cohort comprised workers who had been employed for at least 1 year between 1 January 1972 and 31 December 1995. Complete work histories for the Austrian workers were abstracted from company registries and from the regional social insurance. Information on tobacco smoking habits was obtained from earlier unpublished studies of mortality and pneumoconiosis, from colleagues and from records of the compensation claim insurance. Talc from two of the three Austrian plants (Sites B and C) had a content of quartz that was less than 4%, while that of the third plant (Site D) had higher but unspecified levels. Vital status of workers was verified through to 1995, and cause of death for those who had died was obtained from national mortality files. Local mortality rates yielded an overall SMR for the Austrian cohort of 0.8 (67 observed; 95% CI, 0.6–1.0;). A total of 17 deaths were due to cancer at any site (SMR, 0.7; 95% CI, 0.4–1.2), seven of which were from cancer of the lung (SMR, 1.1; 95% CI, 0.4–2.2). One death from stomach cancer (SMR, 0.4; 95% CI, 0–2.3) and no deaths from mesothelioma (0.1 expected) occurred. On the basis of 23 lung cancer deaths observed in the French cohort in 1968–96 and seven in the Austrian cohort in 1972–95, a nested case–control study was conducted. A total of 88 control subjects were selected from the two cohorts, individually matched to cases on age, calendar period and company. All job tasks at the companies were categorized according to measured and estimated levels of talc dust into one of four

exposure groups (no exposure, < 5 mg/m^3, 5–30 mg/m^3 and > 30 mg/m^3). Job histories of cases and controls were converted into cumulative exposure to talc dust by summing the products of duration and level of exposure for each of the tasks held by the subject (mg/m^3–years). Subjects were also categorized according to tobacco smoking habits, exposure to quartz or a history of underground work on a yes/no basis. Information on smoking habits was available for approximately 50% of the cases and 75% of the controls in the French cohort and for 100% of the Austrian cohort. When the no-exposure category was used as the standard (nine cases, 23 controls), the unadjusted odds ratios for lung cancer were as follows: 0.9 (exposure category, 1–100 mg/m^3–years; six cases, 18 controls); 1.1 (exposure category, 101–400 mg/m^3–years; seven cases, 15 controls), 0.6 (exposure category, 401–800 mg/m^3–years; five cases, 21 controls) and 0.7 (exposure category, > 801 mg/m^3–years; three cases, 10 controls). Assuming a linear trend, the odds ratio was 1.0 (95% CI, 0.9–1.1) per unit of 100 mg/m^3–years. Adjustment for tobacco smoking, exposure to quartz or underground work or any two of these variables did not change the results.

Coggiola *et al.* (2003) updated the cohort of Rubino *et al.* (1976, 1979) to include 1974 men who had worked for at least 1 year in the mine and/or in the factory during the period 1946–95. The mortality analysis included 1795 subjects (90.9% of the total cohort; 1244 miners and 551 millers), after excluding 179 workers who were lost to follow-up. No data on smoking habits were available. Follow-up began on 1 January 1946 or the date of first employment and ended at the date of death or 31 December 1995, during which time a total of 880 deaths occurred. The expected number of deaths was calculated from national rates for 1950–69 and regional mortality rates for 1970 onwards (with the exception of cancers of the oral cavity and oesophagus for which regional rates were unavailable; national rates were therefore used). Rates for the early 1950s were applied for the period 1946–49. Total mortality among workers was higher than expected (880 observed; SMR, 1.2; 95% CI, 1.1–1.3), mainly due to excess mortality from non-malignant respiratory tract diseases among the subgroup of miners (105 observed; SMR, 3.1; 95% CI, 2.5–3.7). Of the 105 deaths in this category, 58 were from silicosis. In the combined cohort of workers, there was no excess mortality for all cancers (185 observed; SMR, 1.0; 95% CI, 0.9–1.1) or for lung cancer, in particular (44 observed; SMR, 0.9; 95% CI, 0.7–1.3). No deaths from pleural or peritoneal mesothelioma were found. A significantly elevated risk was seen for cancers of the oral cavity (31 observed; SMR, 5.1; 95% CI, 3.5–7.3) and the oesophagus (10 observed; SMR, 2.1; 95% CI, 1.1–3.9). When the analysis was stratified by job, the SMR for lung cancer was 1.1 (33 observed; 95% CI, 0.7–1.5) among miners and 0.7 (11 observed; 95% CI, 0.3–1.2) among millers. The slight excess found among miners seemed to be due to a slightly elevated risk in workers with less than 20 years since first exposure (latency) (six observed; SMR, 1.1; 95% CI, 0.4–2.3) compared to that of workers with 20–30 years (10 observed; SMR, 1.0; 95% CI, 0.5–1.8) and more than 30 years (28 observed; SMR, 0.9; 95% CI, 0.6–1.3) since first exposure. There was no variation in lung cancer mortality by duration of exposure. Cancer of the oral cavity caused the death of 24 miners (SMR, 6.2; 95% CI, 3.9–9.1) and

seven millers (SMR, 3.3; 95% CI, 1.3–6.9) and oesophageal caused the death of seven miners (SMR, 2.3; 95% CI, 0.9–4.8) and three millers (SMR, 1.8; 95% CI, 0.4–5.2). Excess mortality was seen in miners for non-malignant respiratory tract diseases (105 observed; SMR, 3.1; 95% CI, 2.5–3.7), non-malignant digestive tract diseases (50 observed; SMR, 1.4; 95% CI, 1.0–1.8) and liver cirrhosis (37 observed; SMR, 1.8; 95% CI, 1.3–2.5). An increased risk for liver cirrhosis was also observed in millers (18 observed; SMR, 1.7; 95% CI, 1.0–2.7).

Meta-analysis of risk for lung cancer

Wild (2006) performed a meta-analysis of lung cancer mortality among miners and millers from industries that produced non-asbestiform talc in Vermont, USA (Selevan *et al.*, 1979), Norway (Wergeland *et al.*, 1990), Italy (Coggiola *et al.*, 2003), France (Wild, 2000) and Austria (Wild *et al.*, 2002). The purpose of the analysis was to compute risk estimates separately for talc miners, who usually have some co-exposure to silica and/or radon daughters, and talc millers, who normally have no such co-exposure. Previously unpublished risk estimates for the subgroup of millers in the French and Austrian cohorts were used and additional information on smoking habits was obtained for Italian, French and Austrian workers. Data indicated that the prevalence of smoking was higher than that in the reference populations [figures not specified]. In the estimation of the overall risk for millers, data from all five countries were used, while only data from the USA, Norway and Italy were included in that for miners. Based on SMRs for lung cancer of 1.0 (USA; two cases; 95% CI, 0.1–3.7), 0.7 (Italy; 11 cases; 95% CI, 0.3–1.2), 1.2 (France; 21 cases; 95% CI, 0.8–1.9), 0.7 (Austria, Site B; three cases; 95% CI, 0.1–2.0) and 1.1 (Austria, Site C; one case; 95% CI, 0–6.2) and an SIR of 0.8 (Norway; four cases; 95% CI, 0.2–2.0) for talc millers, a summary SMR of 0.92 (42 cases; 95% CI, 0.7–1.3) was obtained. No heterogeneity between studies was detected. Similarly, based on mortality ratios for lung cancer of 4.4 (USA; five cases; 95% CI, 1.4–10.2) and 1.1 (Italy; 33 cases; 95% CI, 0.7–1.5) and an incidence ratio of 1.6 (Norway; two cases; 95% CI, 0.2–5.7) for talc miners, a summary SMR of 1.2 (40 cases; 95% CI, 0.9–1.6) was found. Due to a significant heterogeneity of the latter data set, a random effect estimate of the overall SMR was also calculated (40 cases; SMR, 1.9; 95% CI, 0.7–5.1).

2.1.2 *User industries* (Table 2.2)

Information on risk for cancer among workers exposed to talc is available from studies that were conducted in user industries. However, they are less informative than those conducted in talc miners and millers because the potential contamination of talc was not addressed. In addition, these studies provided no details about the type of talc used.

(a) Manufacture of ceramic plumbing fixtures

Thomas and Stewart (1987) conducted a cohort mortality study of 2055 white men employed for at least 1 year between 1939 and 1966 at three plants of a single company in

Table 2.2. Cohort studies of mortality from and incidence of cancer in workers occupationally exposed to non-asbestiform talc in user industries

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors; comments
Manufacture of ceramic plumbing fixtures							
Thomas & Stewart (1987), USA, 5 plants in 1 company	2055 white men employed >1 yearm 1939–66; mortality follow-up through to 1 Jan. 1981; vital status, 96%	Exposure to silica and talc assessed qualitatively by job title–department by industrial hygienist				**SMR**	Crystalline silica was the major exposure; also exposure to non-fibrous and fibrous talc
			All causes	Total cohort	587	0.9 [0.8–1.0]	
			Lung cancer	Total cohort	52	1.4 [1.1–1.9]	
				High silica	44	1.8 [1.3–2.4]	
				High silica+non-fibrous talc	21	2.5 [1.6–3.9]	
				High silica+non-fibrous talc+fibrous talc	5	1.7 [0.6–4.0]	
				High silica+no talc	18	1.4 [0.8–2.2]	
Manufacture of pulp and paper							
Langseth & Andersen (1999), Norway, 10 paper mills	4247 women employed >1 year, 1920–93; follow-up of cancer incidence, 1953–93					**SIR**	Comparison with 5-year age-specific rates in Norwegian women; cancer incidence from National Cancer Registry
			All cancers	Total cohort	380	1.2 (1.1–1.3)	
			Ovarian cancer		37	1.5 (1.1–1.2)	
				Exposure ≥3 years	31	1.6 (1.1–2.3)	
				Age 25–35 years	6	8.0 (2.9–17.4)	
			Ovarian cancer	Paper mill workers	18	2.1 (1.3–3.4)	

Table 2.2 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors; comments
Langseth & Kjaerheim (2004), Norway, 10 paper mills	Nested case–control study in cohort of Langseth & Andersen (1999); 46 cases, 179 matched controls; 100% histologically confirmed	Exposure to asbestos, talc and total dust from work histories, questionnaires by industrial hygienists/ senior employees and international database; personal use of talc: 76% of cases, 57% of controls; personal interviews	Ovarian cancer	Total dust Ever talc Ever asbestos Asbestos according to interview		**Odds ratio** 0.8 (0.4–1.7) 1.1 (0.6–2.2) 2.0 (0.7–5.7) 2.2 (0.5–9.1)	Parity, breastfeeding, tobacco smoking habits, family history of breast or ovarian cancer; conditional logistic regression; odds ratios unchanged after adjustment for confounders
Rubber manufacturing industries							
Blum *et al*. (1979), USA, 2 rubber companies	Nested case–control study; 100 cases, 4 controls per case; matched on age, race, sex, company; 1964–73	Exposure to polycyclic hydrocarbons, nitrosamines, carbon black, talc (high, moderate, low, none) from job histories	Stomach cancer	*Company A* High+moderate talc High talc	 27 13	 2.4 (1.4–4.1)* 1.3 (0.9–2.5)*	No information on composition or purity of talc; no increase in risk in Company B *90% CI

Table 2.2 (contd)

Reference, location	Cohort description	Exposure assessment	Organ site	Exposure categories	No. of cases/ deaths	Relative risk (95% CI)	Adjustment factors; comments
Straif *et al.* (1999), Germany, 5 rubber production plants	8933 male blue-collar workers hired after 1 Jan. 1950 and alive 1 Jan. 1981; follow-up, 1 Jan. 1981 to end of 1991; cause of death known for 97% of 1521 deceased	Work histories recontructed from cost centre codes	Lung cancer Stomach cancer		154 44	**SMR** 1.2 (1.0–1.4) 1.2 (0.8–1.6)	SMRs calculated from national death rates
Straif *et al.* (2000), Germany, 5 rubber production plants	Same as that of Straif *et al.* (1999)	Same as Straif *et al.* (1999) plus semi-quantitative cumulative exposure (low, medium, high) to asbestos, talc, nitrosamines, carbon black for 95% of cohort	Lung cancer Stomach cancer Laryngeal cancer	High talc Medium talc High talc Medium talc High talc Medium talc	21 41 11 12 3 2	1.9 (1.1–3.1) 1.1 (0.8–1.6) 4.3 (2.1–9.0) 1.2 (0.6–2.4) 5.4 (1.1–27.0) 2.8 (0.5–16.7)	Unadjusted; reference: low exposure to talc

CI, confidence interval; SIR, standardized incidence ratio; SMR, standardized mortality ratio

the USA that manufactured ceramic plumbing fixtures. Crystalline silica was said to be the major occupational exposure of these workers, but, in some parts of the plant, exposure to fibrous [tremolitic] and non-fibrous [tremolite-free] talc had also occurred. Vital status was ascertained for 96% of the cohort through to 1 January 1981 and observed numbers of deaths were compared with numbers expected from cause-specific mortality rates for white men in the USA. For each job title–department combination, exposure to silica and talc were qualitatively assessed by an experienced industrial hygienist. Silica exposure was categorized as none, low or high; high exposure to silica was further categorized on the basis of no exposure to talc, exposure to fibrous talc and exposure to non-fibrous talc. The SMR for all causes combined was 0.9 (578 observed [95% CI, 0.8–1.0]) and that for lung cancer was 1.4 (52 observed [95% CI, 1.1–1.9]). The excess mortality from lung cancer was seen exclusively among workers who had been exposed to high levels of silica dust (44 observed; SMR, 1.8 [95% CI, 1.3–2.4]) and, to a greater extent, in the subgroup with additional exposure to non-fibrous talc (21 observed; SMR, 2.5 [95% CI, 1.6–3.9]) than in subgroups with additional exposure to fibrous talc (five observed; SMR, 1.7 [95% CI, 0.6–4.0]) or no exposure to talc (18 observed; SMR, 1.4 [95% CI, 0.8–2.2]). [The Working Group noted that all jobs that involved exposure to talc also involved high exposure to respirable silica.]

(b) Manufacture of pulp and paper

Langseth and Andersen (1999) examined cancer incidence among a cohort of 4247 women who had been employed for at least 1 year between 1920 and 1993 in the Norwegian pulp and paper industry. The women had worked mainly in paper sorting and packing departments in 10 paper mills or in administration (85% of the cohort). Production was judged to involve occupational exposures that included paper dusts, microbes, formaldehyde, talc and asbestos (the latter was used as insulation material in boilers and in the breaks of various rolling machines), but no measurement data were available. Women were followed for cancer incidence between 1953 and 1993 and SIRs were calculated by comparing the observed incidence to the 5-year age-specific incidence rates for the female population of Norway. Information on cancer incidence was obtained by linkage with the National Cancer Registry and information on dates of death and emigration was obtained from the Central Bureau of Statistics of Norway. Records of women who died between 1953 and 1960 were identified manually. Between 1953 and 1993, 535 women in the cohort had died, 65 women had emigrated and 380 new cases of cancer had been diagnosed. The SIR for all cancers was 1.2 (380 observed; 95% CI, 1.1–1.3). An excess of ovarian cancer diagnoses was observed (37 observed; SIR, 1.5; 95% CI, 1.1–2.1). In the analyses, workers were also stratified by exposure into the following categories: short-term (< 3 years) versus long-term (≥ 3 years); period of first exposure (1920–39, 1940–59, 1960–74, 1975–93); and time since first exposure (3–14 years, 15–29 years, ≥ 30 years). The excess risk was predominantly seen among women who had been employed in the industry for 3 years or more (31 observed; SIR, 1.6; 95% CI, 1.1–2.3). The excess risk for ovarian cancer was also highest for women under the age of

55 years at diagnosis, with an SIR of 8.0 (six observed; 95% CI, 2.9–17.4) for women aged 25–35 years at diagnosis. Among women who worked in the paper mills, the SIR for ovarian cancer was 2.1 (18 observed; 95% CI, 1.3–3.4). In the discussion, the authors noted that talc is added as a filler in paper mills and may contribute to the excess risk for ovarian cancer observed.

On the basis of an extended follow-up of cohort members for cancer incidence to the end of 1999, Langseth and Kjaerheim (2004) conducted a nested case–control study that included 46 employees who had ovarian cancer and 179 controls individually matched to cases by incidence density sampling. An experienced oncologist reviewed the pathology for all cases. Work histories were obtained from personnel records at each mill. Exposure to asbestos, talc and total dust was assessed on the basis of the work histories, questionnaires on production processes completed by industrial hygienists and senior employees, as well as semiquantitative exposure assessments for the 10 mills extracted from an international database of exposure in the pulp and paper industry. Information on possible confounders (including use of talc on sanitary napkins, underwear or diapers) was obtained for 76% of cases and 57% of controls through a personal interview with the study subject or next of kin. Odds ratios for ovarian cancer were derived by conditional logistic regression. Ever exposure to asbestos was associated with a non-significantly increased odds ratio for ovarian cancer of 2.0 (95% CI, 0.7–5.7), while ever exposure to talc (odds ratio, 1.1; 95% CI, 0.6–2.2) or to total dust (odds ratio, 0.8; 95% CI, 0.4–1.7) was associated with risks that were close to unity. Among women who were interviewed, the odds ratio for exposure to asbestos was 2.2 (95% CI, 0.5–9.1). This estimate was unchanged after adjustment for multiple potential confounders, including parity, breastfeeding, tobacco smoking habits and family history of breast or ovarian cancer. The odds ratios for occupational exposure to talc and total dust were similarly unchanged after adjustment for confounding.

(c) Rubber manufacturing industries

Following the finding of an excess risk for stomach cancer in a cohort of rubber workers in the USA, Blum *et al.* (1979) carried out a nested case–control study of stomach cancer. Cases were defined as deaths from stomach cancer in two of the rubber companies from 1 January 1964 to 31 December 1973 (100 deaths in total). Four controls were matched to each case on age, race, sex and company. Using the recorded job history of each worker, the investigators and a group of environmental scientists assessed the potential for exposure (high, moderate, low or none) in each job to the following substances: polycyclic hydrocarbons, nitrosamines, carbon black and detackifiers (anti-sticking agents which were mainly talc). No information was available on the purity or composition of the talc (i.e. whether it contained asbestiform materials or other fibrous or non-fibrous carcinogens). While no clear elevation of odds ratio was reported in Company B, a significantly increased relative risk of 2.4 (27 observed; 90% CI, 1.4–4.1) was found in Company A when workers with moderate and high exposure to talc were

pooled into one group. High exposure in the latter company was associated with a modest increase in relative risk of 1.3 (13 observed; 90% CI, 0.7–2.5).

Based on the employment files of five rubber production plants in Germany, Straif *et al.* (1999) conducted a mortality cohort study of 8933 male blue-collar workers who were hired after 1 January 1950 and who were alive on 1 January 1981. Follow-up was started on the date of completion of 1 year of employment or 1 January 1981, whichever came last, and ended on at death, at 85 years of age, at the date of loss to follow-up or 31 December 1991, whichever came first. Cause of death was obtained for 97% of 1521 deceased workers. Work histories were reconstructed from cost centre codes and were classified into six work areas. SMRs were calculated from national death rates and were estimated at 1.2 (154 observed; 95% CI, 1.0–1.4) for lung cancer and 1.2 (44 observed; 95% CI, 0.8–1.6) for stomach cancer. In a subsequent analysis (Straif *et al.*, 2000), information on work history was combined with semiquantitative levels of exposure to asbestos, talc, nitrosamines and carbon black that were estimated by industrial hygienists to yield overall estimates of cumulative exposure (low, medium, high) for approximately 95% of the cohort. Talc is widely used in rubber production and, according to the authors, asbestos was used in all five plants at least until the early 1980s. In risk analyses that were unadjusted for exposure to asbestos or other potential workplace confounders, high and medium occupational exposure to talc were associated with relative risks for lung cancer of 1.9 (21 observed; 95% CI, 1.1–3.1) and 1.1 (41 observed; 95% CI, 0.8–1.6), respectively, when workers with low exposure were used as the reference group. Equivalent risk estimates were 4.3 (11 observed; 95% CI, 2.1–9.0) and 1.2 (12 observed; 95% CI, 0.6–2.4) for stomach cancer and 5.4 (three observed; 95% CI, 1.1–27.0) and 2.8 (two observed; 95% CI, 0.5–16.7) for laryngeal cancer. Separate risk analyses with adjustment for potential confounders were not performed. [The Working Group noted that risk analyses that adjusted for estimates of exposure to asbestos were not presented.]

2.1.3 *Community-based studies*

Chen *et al.* (1992) conducted a case–control study in Beijing, China, of several risk factors for ovarian cancer that included occupational exposure to talc. A total of 220 cases of newly diagnosed epithelial ovarian cancer were identified between 1984 and 1986 through the Beijing Cancer Registry. Of these, 67 [30.5%] were excluded due to death, 37 [16.8%] due to unavailability of current contact information and four [1.8%] due to patient refusal. The analysis was carried out on 112 cases and 224 community controls, with two age-matched controls per case. Potential controls were excluded if they had a history of serious illness, although the percentage of those excluded for this reason was not specified. In addition, 15 of the 224 eligible controls initially selected [6.7%] refused to participate in the study and were therefore replaced by other eligible controls. No information was provided on the age range of the cases and controls, although the mean age at the time of interview was similar for cases (48.5 years) and controls (49.0 years).

All cases were confirmed by laparotomy and pathological review. Data were collected in-person by trained interviewers. Odds ratios were estimated using conditional logistic regression adjusted for education and parity. Occupational exposure to talc was associated with an odds ratio for ovarian cancer of 0.9 (95% CI, 0.3–2.9). [The Working Group noted the incomplete ascertainment of cases of ovarian cancer due to the nature of the cancer-reporting system in China, the large number of cases who were excluded due to death and the exclusion of controls who had a history of serious health problems, which may have resulted in selection bias.]

Hartge and Stewart (1994) analysed the occupational histories of 296 women aged 20–79 years who were diagnosed with ovarian cancer between 1978 and 1981 in the Washington DC area of the USA and 343 hospital-based controls matched to cases on age and race. Pathology was confirmed for all cases. Trained interviewers used a standardized questionnaire to obtain information from each participant on their lifetime job history and occupational exposure to talc. An industrial hygienist blinded to the case status of each participant evaluated each industry and occupation for potential exposure to talc, ionizing radiation, polycyclic aromatic hydrocarbons and solvents, using a scale of 0 (definitely not exposed) to 4 (definitely exposed). Women were considered to be exposed if they had an exposure rating of 2–4 (possibly, probably or definitely exposed). Logistic regression adjusted for race, age, parity, gynaecological surgery and duration of employment in jobs with the exposure of interest was used for the analyses. Controlling for additional known and potential risk factors for ovarian cancer, including parity, oral contraceptive use and cigarette smoking, did not change these estimates. Women who were classified as having been occupationally exposed to talc had odds ratios below the null, although the confidence limits were wide due to the small number of exposed women (12 cases, 31 controls). For women with 10 or more years of employment in an occupation with possible, probable or definite exposure to talc, the odds ratio was 0.5 (five exposed cases; 95% CI, 0.2–1.5). The risk for ovarian cancer was not significantly elevated for any exposure or duration of employment assessed. [Limitations of this analysis include the small number of women occupationally exposed to talc.]

'Industrial talc' was one of the substances evaluated by the exposure assessment team in the community-based case–control study carried out in Montréal, Canada (Siemiatycki, 1991) and described in detail in the monograph on carbon black. About 5% of the 4263 study subjects was considered to be exposed to industrial talc, mostly in the following occupations: painters, motor vehicle mechanics and farmers. Exposure to talc was analysed in relation to 11 different types of cancer, at two levels of exposure (any or substantial). No statistically significant increases in risk were observed. The odds ratios for lung cancer were 0.9 (35 exposed cases; 90% CI, 0.6–1.4) for 'any exposure' and 0.9 (nine exposed cases; 90% CI, 0.5–1.9) for 'substantial exposure'. Prostate cancer was the only site with a borderline significant increased risk, with an odds ratio of 1.4 (29 exposed cases; 90% CI, 1.0–2.1) for 'any exposure' and 1.1 (seven exposed cases; 90% CI, 0.5–2.3) for 'substantial exposure'. [The main limitation of the study was the reliance on expert opinions of exposure rather than measurements for exposure

assessment. Also, exposure levels tend to be lower in such community-based studies than in the workplaces that are selected for cohort studies. The main advantages were the availability of histologically confirmed incident cases and detailed information on tobacco smoking habits and other characteristics of the subjects.]

2.2 Cosmetic use of talc

This evaluation was limited to ovarian cancer because the Working Group was unaware of studies of other cancers associated with the cosmetic use of talc.

The content of body powders used by women varies by product and has changed over time, although data that document this are limited. Before the mid-1970s, body powders may have contained varying but usually small quantities of amphiboles. After that time, amphibole was voluntarily reduced to less than detectable levels, at least in western Europe and the USA. Other non-talc minerals that include chlorite, quartz, carbonates and pyrophyllite may also be found in body powders in varying and occasionally not insignificant quantities in the past and currently. Other added ingredients, which depend on the product, could include cornstarch and perfumes.

2.2.1 *Cohort studies*

Gertig *et al.* (2000) carried out the only prospective cohort analysis that reported an association between perineal use of talcum, baby or deodorant powder and the risk for ovarian cancer. This analysis was conducted among participants in the Nurses' Health Study, a cohort of 121 700 female registered nurses who had been followed since 1976. All participants were between the ages of 30 and 55 years and lived in one of 11 states of the USA at study enrolment. Questionnaires were mailed to participants every 2 years beginning in 1976 to obtain information on the medical history of each woman and potential risk factors for cancer, heart disease and other conditions. The 1982 questionnaire requested information on history and frequency of application of powder to the perineal area (none, daily, one to six times a week, less than once a week) and history of application of powder to sanitary napkins (no/yes). 'Ever talc use' was classified as ever use on either the perineal area or on sanitary napkins. The study population included 78 630 women who responded to the questions on powder use in 1982 and who were not excluded from the analysis for another reason (cancer other than non-melanoma skin cancer before 1982, bilateral oophorectomy, surgery with unknown number of ovaries removed or radiation therapy) and entailed 984 212 person–years of follow-up. Between 1982 and June 1996, 307 incident cases of epithelial ovarian cancer were identified by self-reporting in a biennial questionnaire, by deaths that were reported by relatives or postal authorities or through the National Death Index. Physicians blinded with respect to exposure status reviewed pathology reports to confirm each case and to determine the histological subtype for each tumour as reported by the woman's pathologist. Pooled logistic regression was used to model the incidence rate ratio of ovarian cancer for the

exposed versus unexposed participants. The reported results were adjusted for age in years, parity (defined as the number of pregnancies lasting 6 months or more), duration of oral contraceptive use, body mass index, history of tubal ligation, tobacco smoking status and postmenopausal use of hormones. Additional covariates considered as potential confounders included age at menarche, duration of breastfeeding and age at menopause. Family history of ovarian cancer was not considered to be a confounder, since information on this covariate was not collected until 1992. In 1982, 40.4% of the cohort reported a history of perineal talc use ($n = 31\ 789$) and 14.5% reported a history of daily use ($n = 11\ 411$). Overall, no association between 'ever use' of talcum powder and total risk for epithelial ovarian cancer (relative risk, 1.1; 95% CI, 0.9–1.4) and no trend of increased risk for ovarian cancer with increasing frequency of talc use were observed. However, a modest increase in risk for serous invasive cancers was associated with any history of talc use (relative risk, 1.4; 95% CI, 1.0–1.9) and a borderline significant trend was found with increasing frequency of use (p for trend = 0.05). Among women without a history of tubal ligation, no association was observed between history of talc use and total risk for epithelial ovarian cancer (relative risk, 1.0; 95% CI, 0.7–1.3). Similarly, history of tubal ligation did not modify the association between the use of talc and risk for serous invasive cancers. [Limitations of this analysis include the availability of exposure information at a single time-point only, the relatively short follow-up period after exposure assessment and the lack of information on age at first use of talc, duration of use of talc, current use of talc in 1982 and use of talc before tubal ligation or pregnancy, all of which are potentially important parameters based on previous studies.]

2.2.2 *Case–control studies* (Table 2.3)

Cramer *et al.* (1982) reported the first epidemiological study of genital talc use and the risk for ovarian cancer. The analysis included 215 cases of epithelial ovarian cancer and 215 population-based controls matched to cases by age (within 2 years), race and residence. All cases were Caucasian, English-speaking residents of Massachusetts, USA, aged 18–80 years, who had been diagnosed with epithelial ovarian cancer between November 1978 and September 1981. Cases were identified through pathology logs or tumour boards of 12 participating Boston hospitals. Among 297 eligible cases identified during the time period of interest, 41 were excluded from the study due to: physician refusal (13), patient refusal (14) or death/change of address (14). An additional 41 cases were excluded because they had a non-ovarian primary (18) or a non-epithelial ovarian tumour based on a review of pathology specimens by the authors. Controls were identified though annual listings of the names, addresses and ages of all Massachusetts residents. Among 475 women identified as potential controls, 11.8% (56) could not be reached, 6.1% (29) were ineligible due to previous bilateral oophorectomy, 4.2% (20) were the wrong age, not Caucasian or did not speak English and 32.6% (155) refused to participate. All cases and controls were interviewed in person to obtain information on their medical history, menstrual and reproductive histories, as well as potential for exposure

Table 2.3. Case–control studies of epithelial ovarian cancer (invasive or borderline) and cosmetic use of talc

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Cramer *et al.* (1982) Boston, MA, USA, 1978–81	215 Caucasian, English-speaking women, aged 18–80 years; identified through pathology logs or tumour boards of 12 Boston hospitals; histological confirmation of diagnosis; 215 population-based controls identified through annual listings of names, ages and addresses of all Massachusetts residents; matched by age (±2 years), race, residence	In-person interviews; information collected on medical history, menstrual and reproductive history, potential or definite exposure to talc	'Any' perineal exposure to talc As dusting powder on perineum and sanitary napkins	92 32	1.6 (1.0–2.5) 3.3 (1.7–6.4)	Parity, menopausal status, religion, marital status, educational level, weight, age at menarche, exact parity, oral contraceptive use, postmenopausal use of hormones, tobacco smoking	Distribution of tumour histologies similar for exposed and unexposed cases; potential for talc exposure by way of contraceptives, pelvic surgery or perineal hygiene considered; no information on duration or frequency of talc use; low participation rates among controls (56% of cases matched with no refusals; 27% matched after 1 refusal; 17% matched after 2 or more refusals)
Hartge *et al.* (1983) Washington DC, USA, 1974–77	135 incident cases treated at participating hospitals; 171 population-based controls; frequency-matched by age, race, hospital	Interviews to collect information on reproductive and sexual history, medical history, drug use and other exposures, exposure to talc categorized as 'any' or 'genital' (includes use on genitals, on sanitary napkins or on underwear)	'Any' use of talc 'Genital' exposure to talc	67 7	0.7 (0.4–1.1) 2.5 (0.7–10.0)	Age, race, pregnancy	Questions on talc added after study began; no information on duration or frequency of exposure; no controlling for other potential confounders; potential for selection bias

Table 2.3 (contd)

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Whittemore *et al.* (1988), San Francisco, CA, USA 1983–85	188 incident cases diagnosed at 8 hospitals, aged 18–74 years; histological verification of diagnosis; 539 controls selected from women hospitalized for non-cancerous conditions (*n*=280) or from the population using random digit-dialling (*n*=259); matched by age (±5 years), race, hospital/date of admission (hospital controls) or telephone area code/prefix (population controls)	Structured in-person interviews; information collected on medical history, menstrual and reproductive history, family history, environmental exposures (talc, coffee, alcohol, tobacco); talc exposure categorized by type of application, duration of use prior to tubal ligation or hysterectomy, frequency of use	*Type of application*				No trend of increasing risk with increasing duration of exposure, as measured in years of talcum powder use on the perineum prior to tubal ligation or hysterectomy; non-statistically significant trend of increasing risk with increasing frequency of exposure, as measured in number of applications of talc to the perineum per month
			Perineum only	22	1.5 (0.8–2.6)	Parity, oral contraceptive use	
			Sanitary pads only	5	0.6 (0.2–1.8)		
			Diaphragm only	9	1.5 (0.6–3.6)		
			Any two	67	1.4 (0.9–2.0)		
			All three	1	0.4 (0.0–2.9)		
			Duration of use (years)			Parity	
			None	103	1.0		
			1–9	34	1.6 (1.0–2.6)		
			≥10	50	1.1 (0.7–1.7)		
						Parity	
			Frequency of use				
			Never	97	1.0		
			1–20 times/month	41	1.3 (0.8–2.0)		
			≥20 times/month	44	1.5 (0.9–2.2)		
			30 times/month	–	1.3 (0.9–1.9)		
			p for trend		0.19		

Table 2.3 (contd)

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Booth *et al.* (1989), London and Oxford, United Kingdom, 1978–83	235 incident cases from 15 hospitals, aged 65 years or under at diagnosis; diagnosed within 2 years of interview; histological confirmation of diagnosis; 451 hospital-based controls selected from same 15 hospitals; same age distribution as the cases	Interviewer- administered standard questionnaire; information obtained on reproductive and menstrual history, on exposure to exogenous estrogens, cigarettes, talc; talc exposure categorized by frequency of use on perineum and whether it was used to store a diaphragm	*Frequency of use* Never Rarely Monthly Weekly Daily *p* for trend	 76 6 7 57 71	 1.0 0.9 (0.3–2.4) 0.7 (0.3–1.8) 2.0 (1.3–3.4) 1.3 (0.8–1.9) 0.05	Age, socioeconomic status	Participation rates not provided; questions on talc use added 3 months after start of study; data on talc exposure missing for 18 cases and 17 controls
Harlow & Weiss (1989), western Washington State, USA, 1980–85	116 Caucasian women from 3 urban counties captured in Seattle-Puget Sound Cancer Surveillance System, aged 20–79 years; independent pathological review: 73% of total; histological agreement: 94% of reviewed cases; 158 white population-based controls selected by random-digit dialling; matched by age, county of residence	In-person interviews; information obtained on reproductive, sexual and medical histories, as well as perineal exposure to talc; talc exposure categorized as 'any' perineal use, by method of use, and by type of powder used.	'Any' perineal use *Type of powder used* Cornstarch only Baby powder only Baby powder, combined Talc, unspecified Deodorizing powder only Deodorizing, combined	49 4 18 22 13 10 14	1.1 (0.7–2.1) 0.8 (0.2–3.8) 0.8 (0.4–1.9) 0.9 (0.5–2.0) 1.0 (0.4–2.4) 3.5 (1.2–28.7) 2.8 (1.1–11.7)	Age, parity, use of oral contraceptives	Cases diagnosed with borderline (serous or mucinous) tumours; study limited by incomplete information on powder use and small size; no significant association between method of powder use and risk for borderline tumours

Table 2.3 (contd)

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Chen *et al.* (1992), Beijing, China, 1984–86	112 women from Beijing Cancer Registry, with a mean age of 48.5 years; confirmation of diagnosis by laparotomy and pathological examination in all cases; 224 population-based controls selected first on basis of area of residence of cases and then randomly from census lists of all women within 1 year of age of identified case; matched by age; mean age, 49.0 years	Interviewer-administered questionnaire; information obtained on menstrual, obstetric, marital, medical, family and dietary histories as well as exposure to talc (perineally and occupationally); perineal exposure reported as yes/no	Use on perineum or lower abdomen	7	3.9 (0.9–10.6)	Education, parity	Age range of cases and controls not reported

Table 2.3 (contd)

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Harlow *et al.* (1992), Boston, MA, Massachusetts, USA, 1984–87	235 white women from 10 hospitals in metropolitan Boston area, aged 18–76 years; independent pathological confirmation of diagnosis; 239 population-based controls randomly selected from town registers; matched by age (±2 years), race, precinct of residence; no history of bilateral oopherectomy	In-person interviews; information collected on occupational history, medical and reproductive history, dietary history, tobacco smoking, hygienic practices including perineal exposure to talc; exposure to talc categorized by type of application, brand of powders, duration and frequency of use	'Any' perineal use of talc	114	1.5 (1.0–2.1)	Parity, education, marital status, religion, use of sanitary napkins, douching, age, weight	Odds ratio for women with >10 000 lifetime applications unchanged after excluding applications that occurred after tubal ligation or hysterectomy (odds ratio, 1.7; 95% CI, 1.0–3.0); significant increase in odds ratio for women with >10 000 lifetime applications observed after excluding use of talc during non-ovulatory periods and after surgical sterilization (odds ratio, 2.8; 95% CI, 1.4–5.4)
			Method of application				
			Sanitary napkins or underwear only	9	1.1 (0.4–2.8)		
			Partner or applications to diaphragm	20	1.2 (0.6–2.4)		
			Dusting on perineum	85	1.7 (1.1–2.7)		
			Frequency (no. per month)				
			None	121	1.0		
			<5	32	1.5 (0.8–2.7)		
			5–29	24	1.2 (0.6–2.2)		
			≥30	58	1.8 (1.1–3.0)		
			p for trend		0.046		
			Years of use				
			None	121	1.0		
			<10	14	1.2 (0.5–2.6)		
			10–29	49	1.6 (1.0–2.7)		
			≥30	51	1.6 (1.0–2.7)		
			p for trend		0.07		
			Total applications				
			None	121	1.0		
			<1000	18	1.3 (0.7–2.7)		
			1000–10 000	54	1.5 (0.9–2.4)		
			>10 000	42	1.8 (1.0–3.0)		
			p for trend		0.09		

Table 2.3 (contd)

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Rosenblatt *et al.* (1992), Baltimore, MD, USA, 1981–85	77 women admitted to Johns Hopkins Hospital as in-patients for treatment or diagnosis; diagnosed within 6 months of admission; residents of the USA; pathological confirmation of diagnosis; 46 hospital-based controls selected from female in-patients with no gynaecological or malignant conditions; matched *a posteriori* by age (±5 years), race, closest date of diagnostic admission	Questionnaire administered by telephone and in the hospital; information collected on genital and respiratory exposure to fibre-containing substances, such as talc; sources of genital exposure included contraceptive methods (diaphragm, condoms), dusting of perineum and sanitary products; sources of respiratory exposure included: use of face and/or body powders; residential or occupational exposure to fibre-containing substances, such as talc, asbestos, fiberglass; estimation of 'dose' by adding number of years of exposure from all sources	Genital fibre use *Method of application* Diaphragm use with powder Genital bath talc Sanitary napkin with talc exposure	67 14 22 21	1.0 (0.2–4.0) 3.0 (0.8–10.8) 1.7 (0.7–3.9) 4.8 (1.3–17.8)	Parity Parity, education No adjustment Highest weight, 1 year prior to diagnosis	Investigators encountered difficulty finding controls who met all of the matching criteria. For analysis, 46 matched sets, of which 31 sets had 2 cases and 1 control; limitations include small study size, broad definition of fibre exposure, limited information available on perineal exposure to talc

Table 2.3 (contd)

Reference, study location, study period	Characteristics of cases and controls	Exposure assessment	Exposure categories	No. of exposed cases	Odds ratio (95% CI)	Adjustment for potential confounders	Comments
Tzonou *et al.* (1993), Athens, Greece, 1989–91	189 women hospitalized for ovarian cancer surgery in 2 major cancer hospitals in Greater Athens, aged 75 years or under; histological confirmation of diagnosis; 200 hospital visitor controls (selected from visitors to patients hospitalized in the same wards as cases); not matched to cases by age	Questionnaire administered in hospital by medical residents; information collected on medical and reproductive histories, as well as personal, demographic and socioeconomic variables; qualitative assessment of talc exposure (yes/no use in the perineal region)	*Talc application in perineum* No Yes	 183 6	 1.0 1.1 (0.3–4.0)	Age, education, weight, age at menarche, menopausal status, age at menopause, parity, age at first birth, smoking status, alcohol use, coffee consumption, use of analgesics, use of tranquilizers or hypnotics, use of hair dyes	Study limited by very low prevalence of perineal talc use